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REBOUND INSOMNIA: A CRITICAL REVIEW*

J. C. GILLIN
C. L. SPINWEBER
L. C. JOHNSON

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J. Christian Gillin, M.D. **, ***

Cheryl L. Spinweber, Ph.D. ***

Laverne C. Johnson, Ph.D. ***

** Department of Psychiatry (M003)
University of California, San Diego
San Diego Veterans Administration Medical Center
La Jolla, CA 92093

*** Naval Health Research Center
PO Box 85122
San Diego, CA 92138-9174

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Summary

→ "Rebound insomnia," a worsening of sleep compared to pretreatment levels, has been reported upon discontinuation of short half-life benzodiazepine hypnotics. This paper reviews the existing sleep laboratory studies for the presence or absence of rebound insomnia following treatment with triazolam, temazepam, and flurazepam in insomniac patients or "poor sleepers," and, when possible, in normals.

milligrams
The results indicate that rebound insomnia is a distinct possibility after discontinuation of triazolam in both insomniacs and normal controls. Compared with baseline, disturbed sleep was reported in insomniacs or poor sleepers for the first one or two nights of withdrawal in seven of nine polygraphically recorded sleep studies following triazolam (0.5 mg) and in one of two studies with an adequate number of subjects following triazolam (0.25 mg). In one study conducted in normal volunteers, rebound insomnia was observed following triazolam (0.5 mg) but not triazolam (0.25 mg). In one study, which used subjective reports of sleep rather than polygraphic recordings, rebound insomnia was significantly attenuated after triazolam (0.5 mg) by tapering the dose over four nights. The risk of rebound insomnia after temazepam (15 or 30 mg) was low. In keeping with its long elimination half-life, flurazepam (30 mg) continued to exert beneficial effects for the first two to three withdrawal nights, but the possibility of a mild rebound insomnia cannot be dismissed during the intermediate withdrawal period (nights 4-10) following prolonged, consecutive, nightly administration (more than 30 nights). (KT) ←

The benzodiazepine hypnotics are generally preferred over other types (barbiturates or non-benzodiazepines, non-barbiturates), but there are advantages and disadvantages related to half-life of the benzodiazepines. The risk of rebound insomnia is greater with the short half-life as compared with the long half-life benzodiazepines.

Rebound Insomnia: A Critical Review

J. Christian Gillin, M.D.*/**

Cheryl L. Spinweber, Ph.D.**

Laverne C. Johnson, Ph.D.**

*Department of Psychiatry, UCSD and
San Diego Veterans Administration Medical Center

**Naval Health Research Center

INTRODUCTION

Rebound or withdrawal symptoms are potential problems when discontinuing sedative and anxiolytic drugs. Physical dependence is well documented with high dose, long-term administration of both barbiturates and benzodiazepines in humans (1,2). Fortunately, the frequency of major withdrawal events appears to be low in clinical practice when considering the large number of people receiving prescriptions for these medications (3,4).

More recently, it has been shown that discontinuation of anxiolytics and sedative-hypnotics may produce withdrawal symptoms even if these drugs had been administered at recommended doses (5-12). Different types of symptoms have been described: (a) symptom reemergence, the reappearance of the original symptoms for which the patient originally sought treatment, (b) symptom intensification, an exacerbation of the original symptoms, and (c) symptom creation, the appearance of new symptoms during withdrawal which were not present before treatment (10). For example, symptom reemergence and intensification, and the appearance of new symptoms were shown in a recent, double-blind, placebo-controlled study of patients who had received benzodiazepine doses equivalent to approximately 14-16 mg diazepam for 72-75 months (12). Symptoms occurred earlier following short half-life benzodiazepines compared with long half-life benzodiazepines. Moreover, withdrawal symptoms have also been precipitated in baboons, who had been treated with diazepam for a week, by the administration of RO 15-1788, a specific receptor antagonist of benzodiazepines (13).

In the case of sleeping medicines, Kales and his group have identified two syndromes of disturbed sleep. First, they (14) described a condition which they called "drug-withdrawal insomnia," which occurs following abrupt discontinuation of nonbenzodiazepine hypnotics (i.e., barbiturates, chloral hydrate, etc.,) administered in multiple doses over long periods of time. This syndrome is characterized by increased sleep latency, disrupted and fragmented sleep, and increased dreaming associated with a REM sleep rebound during the withdrawal period. They attributed drug-withdrawal insomnia to the psychological and physiological changes involved in drug discontinuation and considered it part of a general abstinence syndrome resulting from withdrawal of central nervous system (CNS) depressant drugs administered at high doses or for long periods of time.

Kales et al (15-18) later described "rebound insomnia" as a potential problem upon stopping short, half-life benzodiazepine hypnotics which had been taken at recommended doses for even short periods of time. For example, sleep latency and total wake time increased during the early rebound period compared with pretreatment, baseline levels. They interpreted rebound insomnia as a classical withdrawal phenomena, perhaps reflecting up-regulated benzodiazepine recognition sites resulting from receptor blockade.

In the context of prescribing patterns in the United States, Kales and his colleagues singled out triazolam as the primary offending agent in rebound insomnia. Of the three marketed benzodiazepine hypnotics -- triazolam (Halcion), temazepam (Restoril), and flurazepam (Dalmane) -- triazolam has the shortest half-life, with a range of approximately 2-5 hours (19). They considered temazepam, with a half-life of about 10-20 hours, as a potential problem but less than triazolam. Flurazepam, with a pharmacologically active metabolite, desalkylflurazepam, having a half-life of 40-150 hours, was not reported to be associated with rebound insomnia.

Rebound insomnia has been a controversial concept (20-21). In part, the controversy centered around the definition of rebound insomnia. Kales et al (15) originally emphasized increased sleep latency, wake time after sleep onset, and total wake time, but Hartse et al (20) objected that these three measures were not all abnormal in every study. In addition, Nicholson (21)

expressed concern about maintaining the "blind" in studies which concluded with a placebo period, especially where the patient was more likely to recognize placebo substitution following a short half-life compared with a long half-life hypnotic. Finally, Nicholson (21) concluded from his review of available literature at that time, that there was "little or no experimental evidence that proper use of a short-acting hypnotic, triazolam, leads to worsening of sleep on withdrawal, and this is supported by studies with another short-acting drug, temazepam." Moreover, some investigators have suggested that rebound insomnia is not unique to short half-life benzodiazepine hypnotics. It may occur, for example, with long half-life hypnotics such as flurazepam, but at a later time during withdrawal.

Two other problems, possibly related to partial withdrawal from short half-life hypnotics, were also described during the course of nightly administration of triazolam for more than a week or so: increased daytime anxiety (22) and early morning insomnia (23). In this paper, we review the existing literature on rebound insomnia and early morning insomnia for flurazepam, triazolam, and temazepam, concentrating on sleep-laboratory studies of patients with insomnia or who are described as "poor sleepers."

Because sleep often improves spontaneously over time in longitudinal studies of insomnia, a particularly useful research design employs a parallel, independent, placebo-treated group. This design provides both within-group and between-group comparisons for treatment and withdrawal effects. Unfortunately, only a few studies used this design. Therefore, we have usually compared sleep measures during the withdrawal and baseline periods to determine rebound effects. In addition, since tolerance may be related to physical dependence and withdrawal symptoms, we examined sleep during the treatment period.

The specific sleep indices of drug efficacy and rebound insomnia varied from study to study and included total sleep time, sleep efficiency (percent of time in bed spent asleep), sleep latency (time to fall asleep), wake time after sleep onset (WASO), total wake time, and early morning awakening. No single sleep measure was present in all available studies. We concentrated upon total sleep time when this measure was available or could be calculated

from other data provided in the specific study, and refer to other measures such as sleep latency, sleep efficiency, and wake time after sleep onset when these were available.

When data from individual nights during treatment or withdrawal were available, we examined them. Otherwise, we used data from grouped nights (i.e., the average of three recovery nights) when these were available. In order to facilitate comparisons within groups and between groups in this paper, we frequently present specific sleep indices for treatment and withdrawal periods as a percentage of baseline values.

RESULTS

Triazolam

Sleep findings were reviewed in 11 all-night sleep laboratory studies in which triazolam was administered to chronic insomniacs or "poor sleepers" in a placebo-triazolam-placebo design (24-34) (Table 1). Only two of the 11 studies in this review of triazolam used an independent, parallel placebo-treated group (30,33). Duration of treatment ranged from 4-37 consecutive nights. The dose was 0.5 mg in nine studies, 0.25 mg in three studies [3 patients in one study (24), 6 patients each, in two studies (28,34)] and 1.0 mg in one study of 3 patients (24).

In five studies, all of which used a dose of 0.5 mg, data from individual nights were available during either hypnotic treatment or withdrawal (24,25,31-33). In other studies, data were averaged or grouped for specific time periods before, during, and after treatment with triazolam.

Rebound Insomnia

Results from seven of the nine studies on triazolam (0.5 mg) suggested rebound insomnia: Vogel et al (24,26), Roth et al (25), Kales et al (27), Adam et al (31), Mamelak et al (32), and Mitler et al (33) [see also Johnson et al (35)] (see Table 1). In one of these studies, the rebound changes reported were small [see Roth et al (25)]. In two other studies, no

Table 1. Sleep Laboratory Studies of Triazolam* in Chronic Insomniacs or Poor Sleepers

Authors	Subjects	Age	Design	Indices of Rebound				
				TS	SE†	SL	WASO	EMA
Vogel et al 1975 (24)	S+O n=6	29-54	P1-4 T5-11 W12-14	Y	Y	Y	NS	NS
Roth et al 1976 (25)	S n=8	35-55	P1-4 T5-18 W19-22	NS	NS	N	NS	NS
Vogel et al 1976 (26)	S+O n=12	29-63 X=47	P1-3 T3-6 W7-9	Y	N	Y	NS	NS
Kales et al 1976 (27)	S n=7	NS	P1-4 T5-18 W19-22	Y	Y	Y	Y	NS
Roth et al 1977 (28)	S n=6 T=0.25 mg	18-25	P1-4 T5-11 W12-14	N	NS	N	NS	NS
Pegram et al 1980 (29)	S n=6	41-58 X=49	P1-4 T5-25 W26-32	N	NS	N	NS	NS
Spinweber & Johnson 1982 (30)	S+O n=10 PS	21+2	P1-4 T5-10 W11-12	N	N	N	NS	NS
Adam et al 1984 (31)	S n=9 PS	48-69 X=61	P1-14 T15-35 W36-42	Y	NS	Y	Y	N
Mamelak et al 1984 (32)	S+O n=6	32-56 X=45	P1-4 T5-18 W19-25	Y	NS	Y	NS	N
Mittler et al 1984 (33)	S n=7	27-59 X=44	B1-3 P4-13 T14-49 W50-53 W57-59	Y N	Y N	Y N	N N	N N
Kales et al 1986 (34)	S+O n=6 T=0.25 mg	19-65 X=41	P1-4 T5-18 W19-22	NS	N	N	Y	NS

* dose: 0.5 mg unless otherwise stated

TS = Total Sleep time SL = Sleep latency
SE† = Sleep efficiency WASO = Wake time after sleep onset
S = Subjective insomnia
O = Objective insomnia (sleep laboratory criteria)
P = Placebo
n = Number of subjects
T = Triazolam
W = Withdrawal
Y = Rebound insomnia

EMA = Early morning awake time
Anx = Daytime anxiety
NS = Not stated
X = Mean
N = No statistically significant rebound insomnia
PS = "Poor sleeper"
B = Baseline (w/o placebo)

evidence for rebound insomnia was found: Pegram et al (29), and Spinweber and Johnson (30). In the studies reporting rebound insomnia, the specific indices showing deteriorated sleep during withdrawal varied from study to study. Therefore, we present the results for each measure separately (Table 1).

In two studies of triazolam (0.25 mg) each of which employed 6 patients, evidence of rebound insomnia was not found in one study [Roth et al (28)], but was reported in the second in which a significant increase of total wake time occurred for the first three withdrawal nights [Kales et al (34)].

Triazolam (0.5 mg): Changes in Total Sleep Time. The results for total sleep time in studies administering 0.5 mg are shown in Figures 1 and 2, and Table 1.

Triazolam (0.5 mg) significantly increased total sleep time initially compared with baseline values. In the eight studies in which total sleep time was provided or calculated, total sleep increased about 4-10% during the last nights of the drug-treatment period compared to within-group levels at baseline. Tolerance or partial tolerance appeared to develop in nearly all studies. For example, Adam et al (31) reported that total sleep time increased significantly during the first week of treatment; during the third week of treatment, however, it was significantly less compared with the first week and did not differ from pretreatment levels. In the study of Mitler et al (33), which employed a parallel-placebo group, the triazolam group improved significantly by both within-group and between-group comparisons during the first two weeks of treatment. Total sleep time in the placebo-treated, parallel group increased significantly during the study and was only slightly and nonsignificantly below that of the triazolam group from the third to fifth week of the active drug period.

During double-blind, placebo-controlled withdrawal periods, total sleep time was significantly reduced below pretreatment placebo values in six of the nine studies of triazolam (0.5 mg). The biggest reduction of total sleep was on the first night of withdrawal when it ranged from 7.5-10% (26)

EFFECTS OF TRIAZOLAM (0.5 mg) ON TOTAL SLEEP TIME

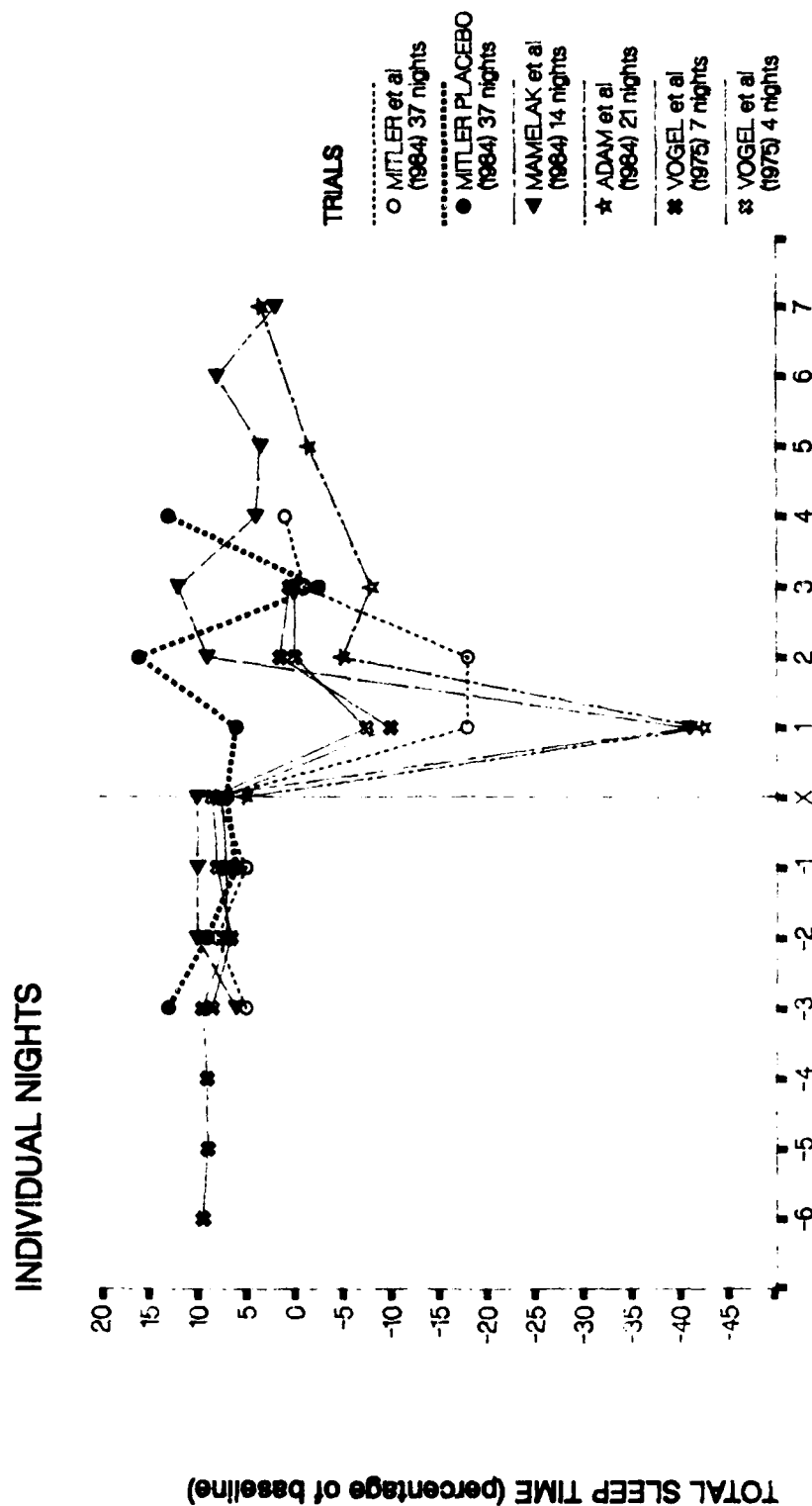
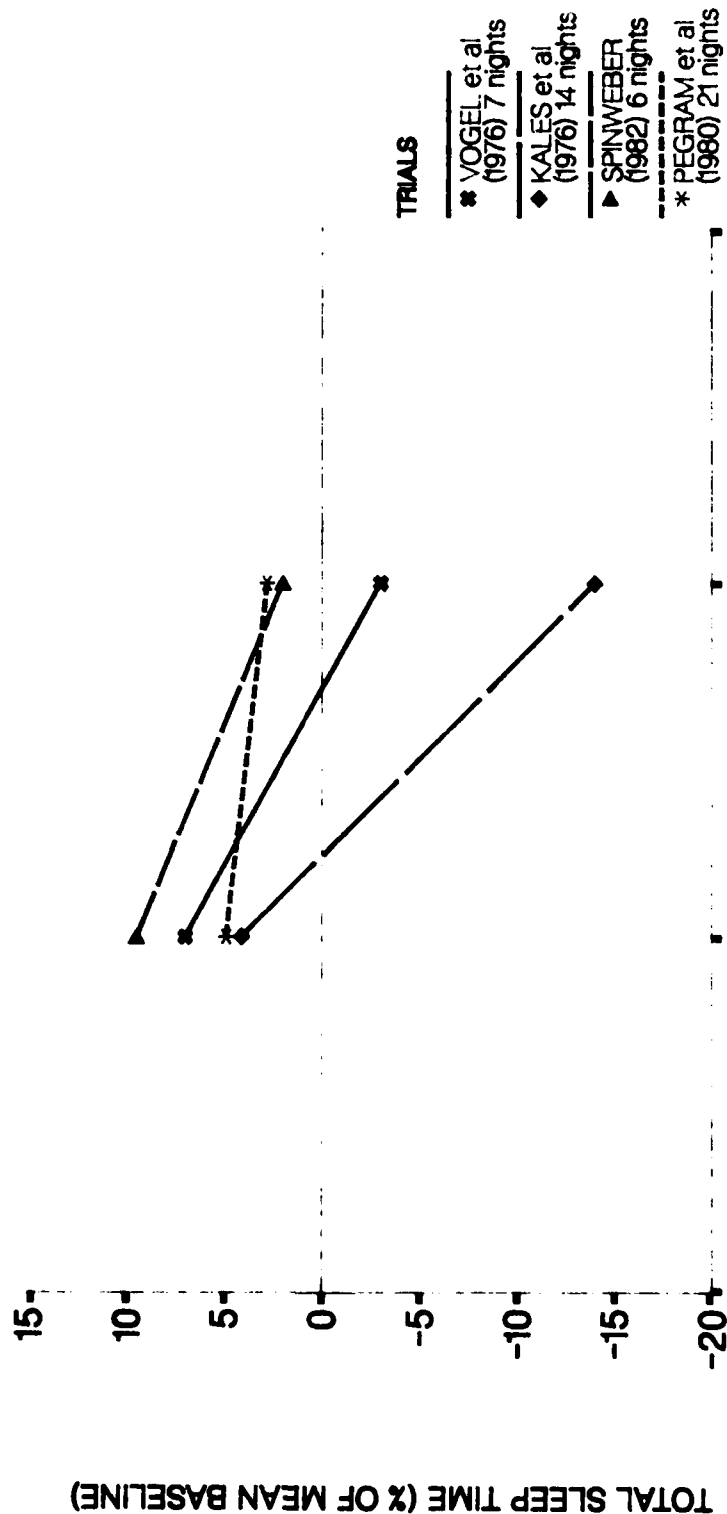


FIGURE 1

EFFECTS OF TRIAZOLAM (0.5 mg) ON TOTAL SLEEP TIME

AVERAGE GROUP NIGHTS



LATE TREATMENT EARLY WITHDRAWAL

FIGURE 2

to about 41-42% below baseline values (31,32). The changes on the first withdrawal night in the study by Mitler et al (33) were in-between, but were statistically significant by both within-group and between-group comparisons. The average reduction of total sleep time in these six studies was 24.5% from baseline or about 85 minutes less sleep on the first night of withdrawal than during pretreatment baseline. On the second and subsequent withdrawal nights, total sleep tended to return to baseline levels or even exceeded it, but considerable variability between studies was noted.

In one of the three studies reporting grouped or mean data for withdrawal nights, Kales et al (27) reported that total sleep time was reduced by about 14% (statistical significance not given) for the three-night withdrawal period compared with baseline. In the other two studies, neither Spinweber and Johnson (30) nor Pegram et al (29) reported a significant change in average total sleep time on the first withdrawal night or during the whole withdrawal period compared with baseline. In addition, Spinweber and Johnson (30) did not find a significant difference between the triazolam-treated group and the parallel, placebo-treated group during withdrawal on a measure reflecting the difference between baseline and withdrawal nights for each subject.

Triazolam (0.5 mg): Other Measures of Rebound Insomnia. Data on sleep efficiency were available in five of the studies reviewed (Table 1). Of the four studies in this group which reported rebound insomnia, three studies showed a significant reduction in sleep efficiency: Vogel et al (24), Kales et al (27), and Mitler et al (33). Vogel et al (26), however, did not find a significant change in sleep efficiency although he did find a significant reduction in total sleep time and an increase in sleep latency.

Data on sleep latency were reported in all nine studies of triazolam (0.5 mg) (Table 1). In the seven studies reporting some evidence of rebound insomnia, sleep latency was significantly increased during early withdrawal in five studies: Vogel et al (24,26), Kales et al (27), Adam et al (31), and Mitler et al (33). Although not statistically significant, mean sleep latency was increased considerably in the study by Mamelak et al (32). Roth et al (25) had the only study reporting no change in sleep latency.

Data on wake time after sleep onset were reported in three studies, all of which reported rebound insomnia. In two of these, it was increased during the first withdrawal nights [Kales et al (27) and Adam et al (31)] but not in the study by Mitler et al (33).

In their study of triazolam (0.5 mg), Roth et al (25) found that stage wake, as a percentage of the night, increased a small but significant amount during the four-night withdrawal period compared with baseline (from 11.3%-12.8%, $p < .05$) but total wake time in minutes was unchanged. They did not report either total sleep time or sleep efficiency; no other measures of rebound insomnia were significant in their study.

In more recent papers, Kales et al (17,18) defined rebound insomnia as a "statistically significant increase or an increase of 40% or greater in the mean group value for total wake time for a single withdrawal night or the entire withdrawal condition as compared with baseline." In the four studies of triazolam (0.5 mg) reviewed in Table 2, total wake time increased during withdrawal on the first withdrawal night or throughout the three-night withdrawal period in three studies [Vogel et al (24,26) and Kales et al (27)]. On the other hand, Spinweber and Johnson (30) found a nonsignificant reduction in total wake time during withdrawal from triazolam (0.5 mg).

Table 2. Changes in Total Wake Time Compared to Baseline in Studies of Withdrawal From Triazolam

Authors	Dose	Withdrawal #1	Withdrawal #1-3
Vogel et al 1975 (24)	0.5 mg	+ 52% ($p < .02$)	+15% ($p < .05$)
Kales et al 1976; 1983 (27)	0.5 mg	+130% ($p < .01$)	+60% ($p < .01$)
Vogel et al 1976 (26)	0.5 mg	+ 48% ($p < .01$)	+20% (p NS)
Roth et al, 1977 (28)	0.25 mg	Not stated	+ 5% (p NS)
Spinweber & Johnson 1982 (30)	0.5 mg	p NS	-18% (p NS)
Kales et al 1986 (34)	0.25 mg	+ 57% ($p < .01$)	+21% (p NS)

p NS - Probability not statistically significant

In an attempt to assess individual differences in rebound insomnia, Bixler et al (36) compared a group treated with triazolam (0.5 mg) for two weeks with a composite group consisting of placebo-treated patients. The rate of rebound insomnia was calculated by determining the number of withdrawal nights in which total wake time exceeded the baseline mean total wake time by two standard errors of the mean. By this definition, the rate of rebound insomnia was significantly higher in the triazolam group than in the placebo group (61.9% versus 13.3%, $p < .01$).

Triazolam (0.5 mg): Comparison with other Parallel Drug-Treated Groups.

Comparison of withdrawal problems between drugs is not definitive evidence for rebound insomnia, but is useful corroborative data for the drug-placebo group studies. In studies where patients treated with flurazepam (26,33), loprazolam (31), and quazepam (32) were compared with patients who had been treated with triazolam, triazolam patients slept significantly worse on a variety of sleep measures during the early withdrawal period. Mitler et al (33) [see also Johnson et al (35)] reported that sleep latency was significantly longer and sleep efficiency significantly worse during the first few days of withdrawal from triazolam compared with both the parallel placebo group and the parallel flurazepam (30 mg) group.

Triazolam (0.25 or 1.0 mg): Dose response data are limited. As mentioned previously, in one study of triazolam at a dose of 0.25 mg for one week in 6 relatively young patients, Roth et al (28) did not find rebound insomnia. In addition, sleep-promoting effects were initially weak and tolerance developed. For example, total sleep time (estimated by summing the stages of sleep) increased by about 4.8% early in the one-week treatment period, by about 2% late in the treatment period, and was virtually unchanged during the three-night recovery period. None of the sleep measures differed from baseline during the last three nights of treatment even though total wake time, Stage 2, and sleep latency were significantly improved during the first three nights. Likewise, none of the sleep measures, including sleep latency and total wake time (Table 2), differed during withdrawal compared with baseline. In a study of somewhat older patients, Kales et al (34) did find evidence of rebound insomnia, as mentioned earlier. Curiously,

these patients showed no significant changes in sleep during either the first or last three nights of the two-week treatment period (Table 2).

Vogel et al (24) found no rebound insomnia in their more limited study of 3 patients who received triazolam 0.25 mg for 7 nights. Vogel et al (24) showed about a 5% increase in total sleep time during treatment and about a 3% reduction during withdrawal. In the same study, the 6 patients who received 0.5 mg showed a similar reduction of about 3% in total sleep during a three-night recovery period. The 3 patients who received 1.0 mg showed a greater rebound insomnia, averaging about 19% less sleep during recovery than baseline (24).

Early Morning Awakening

Kales et al (23) suggested that early morning insomnia increased with nightly administration of triazolam and other short half-life hypnotics after treatment for about one week or more. For example, wake time during the last 2 hours of the night increased from 8.3 ± 12 minutes at baseline to 12.9 ± 7.7 minutes (p NS) on night 12 of treatment with triazolam, 18.1 ± 6.1 minutes ($p < .01$) on night 13, and to 9.5 ± 2.8 minutes (p NS) on nights 14, respectively. The mean wake time during the last 2 hours of those three nights was 13.5 ± 3.3 minutes (p NS). Kales et al (23) also calculated the rate of early morning insomnia by determining the number of times each subject's wake time exceeded baseline values. The rate was significantly higher in the triazolam group than in the combined rates associated with administration of the long half-life hypnotics, flurazepam (30 mg) and quazepam (30 mg), $38.1 \pm 8.7\%$ for the triazolam-treated group versus $9.5 \pm 2.1\%$ ($p < .01$) for the group treated with long half-life drugs.

Of the nine studies of triazolam (0.5 mg), three provided data on early morning awakening (EMA): Adam et al (31), Mamelak et al (32), and Mitler et al (33). None reported increased early morning awakening during treatment, although duration of drug administration ranged from 14-37 nights. In an expanded reanalysis of Mitler et al data (33), Johnson et al (35) reported no significant increase in early morning awakening by the 7 insomniac patients

receiving triazolam (0.5 mg) when compared with either placebo or flurazepam (30 mg) treated patients.

Flurazepam

Ten all-night sleep laboratory studies were reviewed in which flurazepam was administered to chronic insomniacs or "poor sleepers" in a placebo-flurazepam-placebo design (Table 3) (26,33,37-44). The dose was 30 mg per night in nine studies, and 15 mg in one (Roehrs et al (43)). Flurazepam was given for periods ranging from 4-37 consecutive nights.

In three studies, data from individual nights were available for either total sleep time or sleep efficiency during hypnotic treatment or withdrawal (26,33,44). In other studies, data were averaged or grouped for specific times before, during, and after treatment with flurazepam.

Sleep was recorded on the first 2 or 3 nights of withdrawal in all studies. Because of the long half-life issues with flurazepam, several studies also recorded additional, later nights during withdrawal: the first 5 nights (4 patients each in three different groups) [Kales et al (37)], nights 13-15 of withdrawal [Kales et al (38,39)], nights 12-15 [Dement et al (40)], nights 6-7 [Mendelson et al (42)], nights 1-3, 5, and 7 [Adam et al (44)], and nights 1-4 and 8-10 [Mitler et al (33)]. In their 1982 study, Kales et al (41) also gave nightly values for total wake time for 15 consecutive withdrawal nights.

Rebound Insomnia

None of the ten studies showed evidence of rebound insomnia during the early withdrawal period following flurazepam (15 or 30 mg). Nevertheless, there were inconclusive suggestions of a delayed, generally-mild rebound insomnia.

Flurazepam (30 mg): The results for total sleep time are shown in Figures 3 and 4, and Table 3. During the final period of flurazepam treatment, total sleep time was increased in four (26,40,42,44) of the five

Table 3. Sleep Laboratory Studies of Flurazepam^a in Chronic Insomniacs or Poor Sleepers

Authors	Subjects	Age	Design	Indices of Rebound				
				TS	SE%	SL	WASO	EMA
Kales et al 1971 (37)	S n=4 (ea. grp.)	X=31	1.LPPL@	NS	NS	N	N	NS
			2.LPPL@	NS	NS	N	N	NS
			3.LPPL@	NS	NS	N	N	NS
Kales et al 1975 (38)	S N=4	21-53	P1-4					
			P5-32					
			W33-35	NS	NS	N	N	NS
Kales et al 1976 (39)	S n=5-23	NS	W45-57	NS	N	N	N	NS
			p1-4					
			P5-7					
Vogel et al 1976 (26)	S+O n=12	X=47	-18					
			-32					
			W33-35	NS	NS	N	N	NS
Dement et al 1978 (40)	S n=7	36-53 X=45	W45-47	NS	NS	N	N	NS
			P1-2					
			P3-6					
Kales et al 1982 (41)	S=O n=6	22-45 X=45	P7-8	N	N	N	NS	NS
			P1-5					
			P6-33					
Mendelson et al 1982 (42)	S n=10	23-44 X=37	P34-36	N	N	N	N	NS
			W45-47	N	N	N	N	NS
			P1-4					
Roehrs et al 1982 (43)	S n=9 F=15 mg	X=37	P5-32					
			P33-47	NS	NS	N	N	NS
			W45-47	NS	N	N	N	NS
Adam & Oswald 1984 (44)	FS n=9	X=61 54-66	W32-33	N	N	N	NS	NS
			W37-38	N	N	N	NS	NS
			P1-14					
Mitler et al 1984 (33)	S n=7	31-61 X=45	P15-33					
			W36-38	N	N	N	NS	NS
			W40-42	N	N	N	NS	NS
			B1-3					
			P4-12					
			P13-49					
			W50-53	N	N	N	N	N
			W57-59	Y	N	N	N	N

^a dose: 30 mg unless otherwise stated

TS = Total Sleep time SL = Sleep latency EMA = Early morning awake time
 SE% = Sleep efficiency WASO = Wake time after sleep onset Anx = Daytime anxiety
 S = Subjective insomnia
 X = Mean
 L = Lab without drugs
 F = Flurazepam
 P = Placebo
 @ = 5 nights each
 NS = Not stated
 N = No statistically significant rebound insomnia
 n = number of subjects
 W = Withdrawal
 O = Objective insomnia (sleep laboratory criteria)
 FS = "Poor sleepers"
 B = Baseline (w/o placebo)
 Y = Rebound insomnia

EFFECTS OF FLURAZEPAM (30 mg) ON TOTAL SLEEP TIME

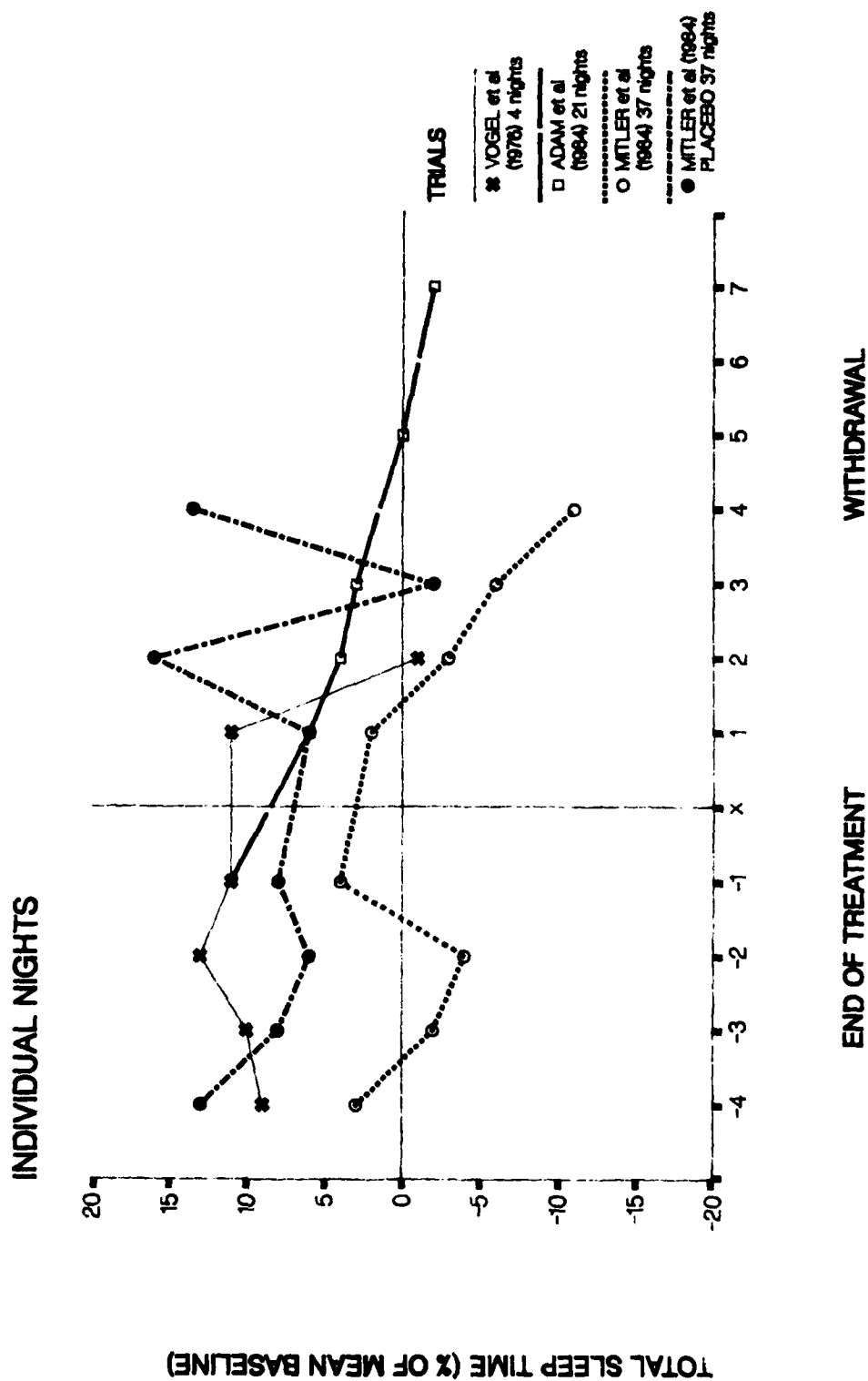


FIGURE 3

EFFECTS OF FLURAZEPAM (30 mg) ON TOTAL SLEEP TIME

AVERAGED NIGHTS

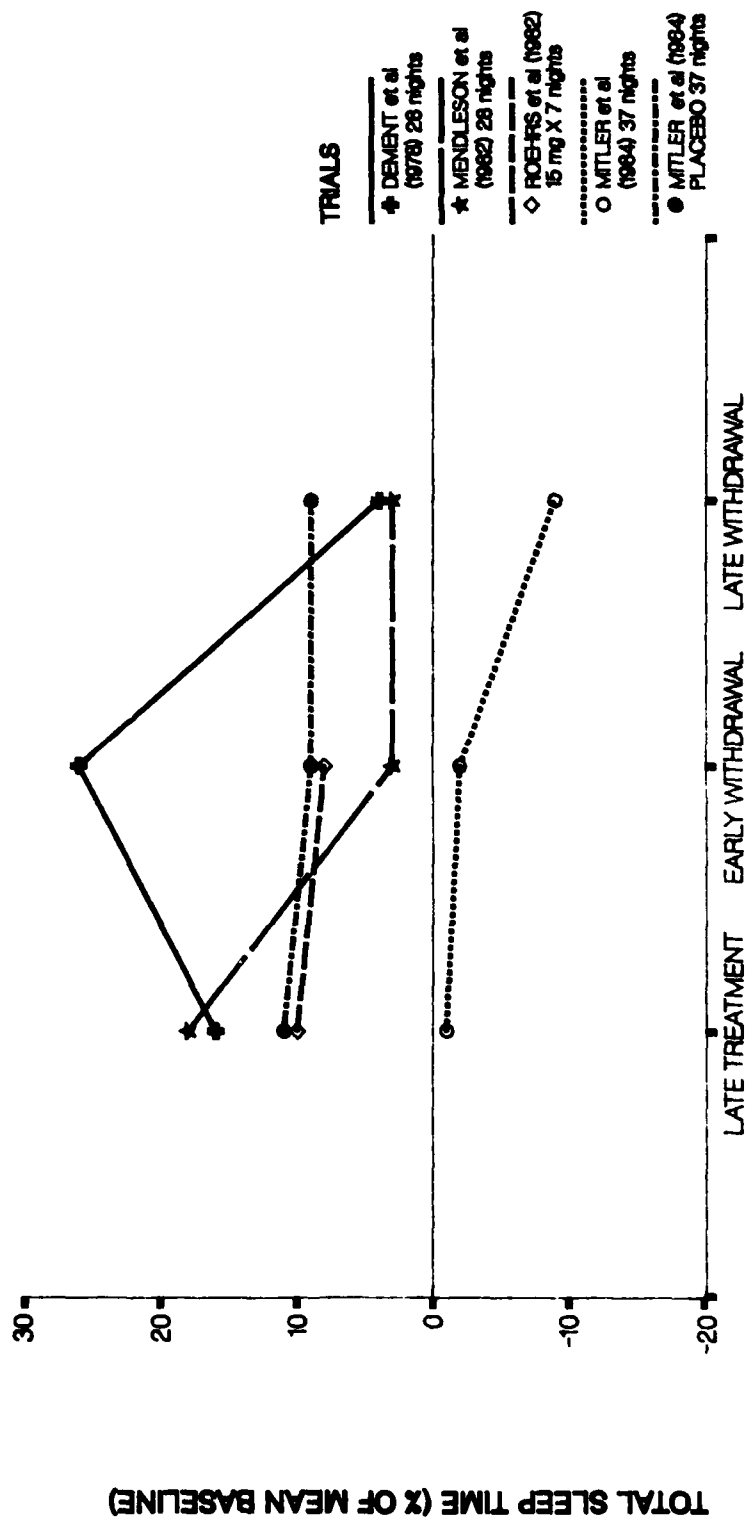


FIGURE 4

studies which reported total sleep time compared with pretreatment placebo administration. In these four studies, total sleep time was increased about 8-18% at the end of the treatment period compared to baseline. In the seventh study, Mitler et al (33) indicated that tolerance apparently developed as both within-group and between-group (placebo) comparisons were not significant. However, significant improvement in total sleep time was present during the first three weeks of treatment as compared with before treatment; at the end of the fifth week of treatment, it was the same as during the pretreatment, placebo period. The placebo, flurazepam, and triazolam groups all had about the same amount of sleep during the fifth week of treatment.

None of the studies reported a significant reduction in total sleep time or any other index of withdrawal insomnia during the first 1-3 nights after flurazepam compared with baseline. Indeed, in many studies, sleep was significantly better on one or more measures during the acute withdrawal period, in keeping with the concept of a long half-life hypnotic.

During more extended withdrawal, evidence of rebound insomnia was weak but present between withdrawal nights 4 and 10 following flurazepam in two studies (33,41) (Table 3). None of the four studies at withdrawal nights 12-15 showed significant evidence for rebound insomnia [Kales et al (37,38,39) or Dement et al (40)]. Nevertheless, at a somewhat earlier time in withdrawal, Mitler et al (33) reported significantly less sleep time during the second week of withdrawal (nights 8-10) compared with both the parallel, placebo group and the triazolam group. During the second week of withdrawal, the flurazepam group slept an average of about 9% less than during baseline prior to treatment (33). However, in a further analysis of this study, Johnson et al (35) found that sleep efficiency at this time was not significantly different from pretreatment placebo values, although it was considerably lower (81.3% versus 88.3%), and from the parallel, placebo group during its second withdrawal week (88.5%) (35). The poor mean sleep efficiency during the second withdrawal week was due to 2 patients who had low values (35). None of the insomniacs in the flurazepam (30 mg) group had a sleep efficiency below 60% during baseline. Four patients, however, did

have low sleep efficiency during withdrawal after 37 consecutive nights of treatment. When sleep was poor, it never occurred before the third night of withdrawal (35).

In their 1982 study, Kales et al (41) presented the only data from consecutive, nightly recordings for the first 15 nights of withdrawal from flurazepam (30 mg). Average total wake time was increased by 21% on the fourth withdrawal night and by 22.2% on the 14th withdrawal night compared with baseline values.

Flurazepam (30 mg): Comparison with other drugs. In comparison with parallel treatment groups during withdrawal, flurazepam patients slept significantly longer during the first 3 nights than patients who had been treated with lormetazepam (either 1.0 or 2.5 mg) (45). In a comparative study with triazolam, flurazepam patients slept significantly better in terms of sleep latency (26,33,35) and sleep efficiency (33,35) than triazolam-treated patients during the first 4 days of withdrawal. In a third study, flurazepam patients slept about the same as patients who had been treated with quazepam (either 15 or 30 mg) over the course of a 15-day withdrawal (41).

In a more extensive review of rebound insomnia (measured by total wake time compared with baseline) during the first 3 days of withdrawal, Kales et al (17,18) concluded that the longer half-life hypnotics, such as flurazepam (30 mg) and quazepam (30 mg), tended to show persistent benefits, whereas significant rebound occurred with flunitrazepam (2 mg), nitrazepam (10 mg), midazolam 20 mg, and triazolam (0.5 mg); other drugs tended to produce little or no significant change, including chloral hydrate (1 gm), ethchlorvynol (500 mg), pentobarbital (100 mg), secobarbital (100 mg), methaqualone (400 mg), and glutethimide (500 mg).

Flurazepam (15 mg): Roehrs et al (43) administered flurazepam (15 mg) to 9 insomniac patients for 7 consecutive nights, followed by 3 placebo nights. Total sleep time was significantly increased during treatment (about 11% on nights 5-7), without evidence of either tolerance during treatment or

rebound insomnia. Sleep time, wake during sleep, and number of awakenings were significantly better during withdrawal than baseline.

Early Morning Awakening

Flurazepam (15 or 30 mg) was not associated with reports of early morning insomnia in the studies reviewed.

Temazepam

Data from four, all-night sleep laboratory studies were reviewed in which temazepam was administered to chronic insomniacs in a placebo-temazepam-placebo design, Table 4 (45-48). Temazepam was given in a dose of 15 mg in two trials [Mitler et al (46), Kales et al (48)] and 30 mg in three trials [Bixler et al (45), Mitler et al (46), Roehrs et al (47)]. Mitler et al (46) studied both 15 mg and 30 mg. Duration of treatment ranged from 9-33 consecutive nights.

Data were averaged for specific periods of the protocol in each of the three studies. Detailed data on individual nights were not presented, although in some studies, reference was made to specific sleep measures on specific nights of withdrawal.

Data on the first three withdrawal nights were presented in all studies. In addition, data were also presented on withdrawal nights 12-14 [Bixler et al (45)] and nights 8-10 [Mitler et al (46)] following temazepam 30 mg.

Rebound Insomnia

No significant evidence was shown for significant rebound insomnia following temazepam at doses of either 15 mg or 30 mg. Nevertheless, some evidence suggests that it may occur in a mild form after the higher dose.

Temazepam (30 mg): Temazepam (30 mg) was more clinically effective in two of the studies (46,47) than in the third (45). Mitler et al (46) reported that it significantly increased total sleep time through the

Table 4. Sleep Laboratory Studies of Temazepam in Chronic Insomniacs or Poor Sleepers

				<u>Indices of Rebound</u>				
<u>Authors</u>	<u>Subjects</u>	<u>Age</u>	<u>Design</u>	<u>TS</u>	<u>SE%</u>	<u>SL</u>	<u>WASO</u>	<u>TWT</u>
<u>Dose: 30 mg</u>								
Bixler et al 1978 (45)	S n=6	22-51	A1-4 P5-7 T8-35 W36-38 W47-49	NS NS	N N	N N	N N	N N
Mittler et al 1979 (46)	n=8	46-66 X=55	P1-9 T10-44 W45-47 W52-54	N N	NS NS	N N	N N	NS NS
Roehrs et al 1984 (47)	S+O n=12	21-46 X=30	P1-4 T5-13 W14-16	N	NS	N	N	N
<u>Dose: 15 mg</u>								
Mittler et al 1979 (46)	S+O n=8	50-58 X=53	P1-9 T10-23 W24-26	N	NS	N	N	NS
Kales et al 1986 (48)	S+O n=6	26-65 X=43	P1-4 T5-18 W19-22	NS	N	N	N	N

TS = Total Sleep time
 SE% = Sleep efficiency
 SL = Sleep latency
 WASO = Wake time after sleep onset
 TWT = Total wake time
 S = Subjective insomnia
 A = Adaptation
 n = number of subjects
 P = Placebo
 T = Temazepam
 W = Withdrawal
 NS = Not stated
 N = No statistically significant rebound
 X = Mean
 O = Objective insomnia

33-night treatment period, with an increase of about 23% above baseline at the end of treatment. Roehrs et al (47) also reported significantly-improved sleep, with an increase in total sleep time of about 10% at the end of the 9-day treatment period. Sleep latency was also significantly reduced in this group of patients who were selected for sleep onset insomnia. Sleep on the last day of treatment was not significantly different from that on the first day of treatment. In contrast, Bixler et al (45) found little hypnotic effect, except for a significant reduction of total number of wakes during the 28-night treatment period.

None of the studies reported a consistent, statistically significant deterioration of sleep during either acute or extended withdrawal from temazepam (30 mg). However, both Mitler et al (46) and Bixler et al (45), reported nonsignificant trends during early withdrawal nights suggesting poorer sleep maintenance. In the study by Mitler et al (46), wake time after sleep onset increased by about 41.5% (p NS) during the early 3-night recovery period compared with pretreatment placebo values; data on individual nights were apparently not examined. In the study by Bixler et al (45), total wake time increased from 66.4 minutes at baseline to 74.6 minutes (p NS) during the first 3 nights of withdrawal and to 93.6 minutes (p NS) on withdrawal nights 12-14. No evidence for significant rebound insomnia was reported on withdrawal nights 8-10 [in the Mitler et al study (46)] or on nights 12-14 [in the Bixler et al study (45)].

Roehrs et al (47) also found no consistent evidence for disturbed sleep for the first 3 nights after discontinuation of temazepam (30 mg). Even though their patients were selected for sleep onset insomnia, sleep latency tended to be better during withdrawal than before treatment. Sleep on the first withdrawal night returned to baseline levels. They found non-significantly shorter sleep (<95% of baseline) in only 4 of 12 patients on 6 of 36 recovery nights studied.

Temazepam (15 mg): The short-term clinical effectiveness of temazepam (15 mg for two weeks) was shown in two studies (46,48). In the first, Mitler et al (46) showed that total sleep time improved significantly by analysis of variance and was about 11% above baseline levels at the end of the 14 nights

of treatment. In the second study, Kales et al (48) found that temazepam significantly decreased wake time after sleep onset, total wake time, and increased sleep efficiency, with apparent partial tolerance for sleep efficiency and total wake time on drug nights 12-14.

During acute withdrawal, neither study reported significant sleep changes consistent with rebound insomnia. However, Kales et al (48) found increases of 11% and 13% in total wake time on the first and fourth recovery nights, respectively (p NS). Wakefulness was significantly increased during the first and second thirds of the first recovery night.

In the only study contrasting temazepam (15 mg) with another hypnotic, Kales et al (48) reported that sleep latency was significantly shorter during the first 3 withdrawal nights in the quazepam group than in the temazepam group.

Early Morning Insomnia

Early morning insomnia has not been reported with temazepam in the studies reviewed.

DISCUSSION

The findings of this review support the general concept proposed by Kales et al (15-17) that rebound insomnia may follow triazolam (0.5 mg and possibly 0.25 mg). No consistent significant withdrawal pattern was observed following temazepam (15 or 30 mg). Rebound insomnia was not reported after flurazepam (15 or 30 mg) during the first 3 nights of withdrawal, but the possibility of a generally mild withdrawal syndrome cannot be dismissed in some patients during withdrawal nights 4-10, especially after prolonged treatment.

In the case of triazolam (0.5 mg), seven of the nine studies reviewed reported a transient rebound insomnia on the first night or two of withdrawal. In the study of Roth et al (25), however, the published data showed only a small nonsignificant increase in total wake time, although it

appears from inspection and calculations based upon their data, that total sleep time was reduced by about an hour on the first withdrawal night. The exact type of insomnia varied from study to study, but for most, the sleep disturbance was characterized by reduced total sleep time and sleep efficiency and increased sleep latency and total wake time.

Two other studies did not find rebound insomnia following triazolam (0.5 mg). The presence or absence of rebound insomnia did not appear to be related either to age or to duration of treatment with triazolam (0.5 mg) (29,30). Even though the subjects in the study by Spinweber and Johnson (30) averaged 21 years and were the youngest of any study reviewed, those in the study by Pegram et al (29) averaged 49 years, similar to the subjects in most of the other studies which did demonstrate rebound insomnia. Rebound insomnia was reported in both the shortest and the longest studies, ranging from 4 nights [Vogel et al (26)] to 37 nights [Mitler et al (33)].

Although Spinweber and Johnson (30) did not report rebound insomnia following administration of triazolam (0.5 mg for 6 nights), inspection of their published data suggests that this conclusion cannot be considered definitive. Both the triazolam group and the parallel, placebo group had a 4-night placebo baseline period prior to treatment, but only the second night was used for comparison with the withdrawal nights since subjects underwent arousal on night 3 and were exposed to subarousal clicks on night 4. Though subjects were randomly assigned, sleep latency was unusually long on night 2 in the triazolam group compared with the parallel control group or to their own sleep latency values on nights 3 and 4. Thus, if Spinweber and Johnson (30) had chosen sleep latency on night 4 for baseline sleep or even an average of nights 2 through 4 as a comparison to the first withdrawal night, rebound insomnia might have been reported. It is of interest, however, that between group Student t-tests, calculated from their published data [Table 2 (30)] for the mean of the 2 placebo withdrawal nights, did not show a statistically significant difference between the triazolam and control groups for sleep latency, wake time (minutes or percent), or sleep efficiency. It would be instructive to examine the comparison between triazolam and control groups on withdrawal night 1, but these data are not available. Although Spinweber and Johnson (30) did not report rebound insomnia, their study

raises an important question -- what are the appropriate pretreatment levels when examining for rebound insomnia. We will return to this problem later and suggest a possible answer.

Rebound insomnia after triazolam (0.25 mg) was reported in one study (34) but not in another (28). The patients in the study reporting rebound insomnia were older and were treated for a longer period of time than those in the other study which did not find rebound insomnia. In a recent study, in healthy normal sleepers (21-35 years old), Roehrs et al (49) administered placebo or triazolam (either 0.25 or 0.5 mg) for 6 consecutive nights. Although both doses reduced total wake time significantly during treatment, significant rebound insomnia (increased total wake time, increased sleep latency and increased latency back to sleep after awakening 2.5 hours from bedtime) occurred following the 0.5 mg dose, not the 0.25 mg dose. These studies show that rebound insomnia may occur in both insomniacs and normal controls. In the case of triazolam (0.25 mg), the risk of rebound insomnia may be greater in middle-aged or older patients who have been treated for at least two weeks compared with young insomniac patients or normal controls treated for a week. Since hypnotics are often recommended in the management of transient insomnia occurring in otherwise healthy, normal sleepers, the apparently low risk of rebound insomnia following triazolam (0.25 mg for up to 7 nights) may be clinically important. Further studies will be reviewed to assess the role of age and duration of treatment.

Rebound insomnia does not appear to be related to either the magnitude of improved total sleep time or to tolerance during treatment. Further, the occurrence of rebound insomnia following treatment with triazolam does not appear to be related to whether or not triazolam improved sleep during treatment. Rebound insomnia occurred in a study in which triazolam (0.25 mg) did not improve sleep in insomniac patients (34). It also failed to occur in a study in which triazolam (0.25 mg) did promote sleep in normals (49) and in a study in which triazolam (0.5 mg) did not help insomniac patients (29).

When triazolam (0.5 mg) is administered, it may be possible to attenuate rebound insomnia by tapering the dose gradually. Greenblatt et al (50) compared 30 patients with insomnia who underwent abrupt discontinuation

following triazolam (0.5 mg for 7 to 10 nights) and 30 patients who were gradually withdrawn (0.25 mg for 2 nights, 0.125 mg for 2 nights, and then placebo) following triazolam (0.5 mg for 7 nights). The former group showed rebound insomnia according to subjective criteria (increased sleep latency, awakenings, and decreased sleep duration); the latter group showed only modest rebound insomnia compared with pretreatment levels.

None of the studies reviewed found major rebound insomnia following withdrawal from either 15 mg or 30 mg doses of temazepam, even after 33 consecutive nights of treatment (30 mg). Nevertheless, in a 33-night study, Mitler et al (46) reported a 41.5% increase in wake time after sleep onset (p NS) for the 3 withdrawal nights following temazepam (30 mg). In addition, Kales et al (48) found significantly increased wakefulness during the first and second third of the first withdrawal night following temazepam 15 mg. Therefore, though the risk may be low, it appears prudent to consider the possibility of rebound insomnia following temazepam and to await the results of future clinical experience and research before concluding that it never happens.

In the case of flurazepam (30 mg), hypnotic benefits continue for 1 to 3 nights of withdrawal. Beyond the first 2 or 3 nights of withdrawal, the likelihood of rebound insomnia appears to be low. Perhaps the strongest suggestion comes from the study of Mitler et al (33) [see Johnson et al (35)], who reported that total sleep time was significantly lower and that sleep efficiency tended to be lower during the second week of withdrawal compared with both baseline and the parallel, placebo group. It may be important that this was the only study in which: (a) flurazepam (30 mg) was administered for more than four weeks, and (b) comprehensive measures of sleep were published on withdrawal nights 8-9. In addition, Kales et al (41), found increased total wake time (from about 100 minutes per night to about 120 minutes) on nights 4 and 14. These observations suggest that rebound insomnia may occur in some patients at some time during the fourth through fourteenth night of withdrawal. Further research is needed to evaluate the probability and clinical significance of rebound insomnia, if any, or otherwise disturbed sleep during the intermediate withdrawal period following flurazepam 30 mg.

In discussing the paper of Mitler et al (33), Kales (51) has argued that the study suffers because time in bed was not controlled and this might account for the findings in the study. A counter argument is that the "real world" situation, where subjects choose how long they wish to stay in bed, is a more realistic method of assessing hypnotic effects. Also, the use of sleep efficiency rather than total sleep time in the analysis took into account the varying time-in-bed for each patient [Johnson et al (35)]. These arguments are not easily resolved.

Data were not available beyond the first three nights of withdrawal following administration of flurazepam 15 mg dose. Based upon these limited data, no rebound insomnia was observed.

In future definitions of rebound insomnia, it seems appropriate to accept significant deterioration in one or more sleep measures such as: increased sleep latency, increased total wake time or wake time after sleep onset, reduced total sleep time, or reduced sleep efficiency. Studies of hypnotic agents, however, ought to report all these variables and their definitions for each. Since time in bed may be an important factor, it should also be included in the data presentation and the investigators should state whether they or the subjects determined it. In addition, full data from individual nights should be statistically analyzed and presented, when appropriate. A sufficient number of withdrawal nights should be included to determine whether delayed rebound insomnia exists.

Furthermore, in addition to analysis of mean differences, a more sensitive approach would be to compare each subject's worst withdrawal sleep nights against his/her worst pretreatment sleep. Within subject comparison of worst pretreatment and withdrawal sleep would help overcome the bias toward rebound insomnia when an average of baseline values are used or when the night prior to actual treatment is used. Bias toward reporting rebound insomnia, especially when within group studies are done, can occur because sleep usually improves during baseline, especially if a placebo is given. In this instance, is the insomnia a symptom reemergence or symptom intensification? In addition, we recommend that future investigations calculate the rate of rebound insomnia amongst subjects, i.e., what

proportion of subjects experienced rebound insomnia according to specified criteria. Such an analysis was done by Johnson et al (35) in their reanalysis of the Mitler et al (33) study with effective results. Bixler et al (36) also focused their analysis on the individual patient's response but they used average baseline values in their withdrawal comparisons.

Early morning insomnia was not the focus of the sleep laboratory studies reviewed here. In the limited data available, early morning insomnia was not reported in most of the studies. However, in view of the published data suggesting this problem, further research is needed to establish the frequency and severity of this and other side effects of short half-life hypnotics.

None of these studies reviewed or investigated the effects of intermittent or occasional use. Results from the current studies where these drugs were administered on a consecutive, nightly basis may not be generalized to this more common intermittent pattern of use.

In choosing the appropriate dose of a benzodiazepine hypnotic, the clinician faces a narrow therapeutic range. For most patients, the upper recommended doses are likely to produce various side effects [for example, rebound insomnia for triazolam (0.5 mg) and daytime hangover effects for flurazepam (30 mg)]. For some patients, the lower doses of triazolam (0.25 mg or 0.125 mg), flurazepam (15 mg), or temazepam (15 mg), may be effective but tolerance may develop more quickly to the lower dose than to the higher dose. Though the data are limited, studies have indicated that rebound insomnia and other side effects are less likely at lower doses.

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<p>"Rebound insomnia," a worsening of sleep compared to pretreatment levels, has been reported upon discontinuation of short half-life benzodiazepine hypnotics. This paper reviews the existing sleep laboratory studies for the presence or absence of rebound insomnia following treatment with triazolam, temazepam, and flurazepam in insomniac patients or "poor sleepers," and, when possible, in normals. The results indicate that rebound insomnia is a distinct possibility on the first and second withdrawal night after triazolam in both insomniacs and normal controls but that it is dose dependent (0.5 mg but not 0.25 mg). The risk of rebound insomnia after temazepam (15 or 30 mg) is low. In keeping with its long elimination half life, flurazepam (30 mg) continues to exert beneficial effects for the first two or three withdrawal nights but the possibility of a mild rebound insomnia cannot be dismissed during the intermediate withdrawal period (nights 4-10) following prolonged consecutive, nightly administration (more than 30 nights). The studies in this review provide limited, inconsistent evidence of increased daytime anxiety and early morning awakening in insomniacs treated</p>				
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nightly with triazolam for more than a week, but not for either temazepam or flurazepam. The Benzodiazepine hypnotics are generally preferred compared with other types (barbiturates or non-benzodiazepine, non-barbiturates), but there are advantages and disadvantages related to apparent half life. The risk of rebound insomnia and, possibly, daytime anxiety and early morning awakening with triazolam (0.5 mg) must be weighed against the disadvantages of long half-life benzodiazepine hypnotics, such as daytime drowsiness and increased interactions with sedative agents.